



Review article

Avian influenza virus ecology and evolution through a climatic lens

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ABSTRACT

Avian influenza virus (AIV) is a major health threat to both avian and human populations. The ecology of the virus is driven by numerous factors, including climate and avian migration patterns, yet relatively little is known about these drivers. Long-distance transport of the virus is tied to inter- and intra-continental bird migration, while enhanced viral reassortment is linked to breeding habitats in Beringia shared by migrant species from North America and Asia. Furthermore, water temperature, pH, salinity, and co-existing biota all impact the viability and persistence of the virus in the environment. Changes in climate can potentially alter the ecology of AIV through multiple pathways. Warming temperatures can change the timing and patterns of bird migration, creating novel assemblages of species and new opportunities for viral transport and reassortment. Water temperature and chemistry may also be altered, resulting in changes in virus survival. In this review, we explain how these shifts have the potential to increase viral persistence, pathogenicity, and transmissibility and amplify the threat of pandemic disease in animal and human hosts. Better understanding of climatic influences on viral ecology is essential to developing strategies to limit adverse health effects in humans and animals.

1. Introduction

Changes in climate can precipitate ecosystem shifts, altering the evolution and ecology of infectious diseases. The mechanisms underlying these changes are often complex and poorly understood. This is especially true for avian influenza virus (AIV), which has played a central role in outbreaks in humans and animals over the past century, including the major influenza pandemics of 1918 (H1N1), 1957 (H2N2), and 1968 (H3N2) (Webster et al., 1992; Belshe, 2005). In China, mortality rates as high as 34% have been reported in humans infected with Influenza A H7N9, a virus that appears to have spread to humans from poultry and/or waterfowl either through direct contact or contact with bird secretions (Chen et al., 2005; Gao et al., 2013; Li et al., 2014; Scotch et al., 2015; Su et al., 2015). The US poultry outbreak of 2015 represents the largest domestic animal disaster in US history, with the death of over 48 million birds through illness or culling, causing a \$3.3 billion loss to the US economy (Greene, 2015). This catastrophic outbreak reinforced the importance of wild migratory

birds, especially birds in the order Anseriformes (e.g. ducks and geese) and Charadriiformes (e.g. shorebirds and gulls) that act as reservoirs for the virus (Krauss and Webster, 2010) and transfer the virus in the intercontinental mixing pot of Arctic summer breeding sites, a dynamic likely to be affected by climate change.

This paper will review current knowledge on AIV ecology through a climatic lens with a focus on East Asia and Beringia. Beringia includes the area between the Lena River in Siberia and the Mackenzie River in Canada south to about the tip of the Kamchatka Peninsula (West, 1998) and is the region with the highest levels of Asia-to-North-America avian host movements (Winker and Gibson, 2010). Beringia is important as a viral transport and mixing zone for AIV (Winker et al., 2007; Koehler et al., 2008; Lee et al., 2015; Lycett et al., 2016). Agriculture and poultry markets in East and Southeast Asia have importance in AIV transmission between domestic and wild bird populations (Muzaffar et al., 2010; Cappelle et al., 2014) and live poultry markets can serve as a route for geographic spread of AIV (Artois et al., 2017). Additionally, climate change and sociodemographic and economic factors are

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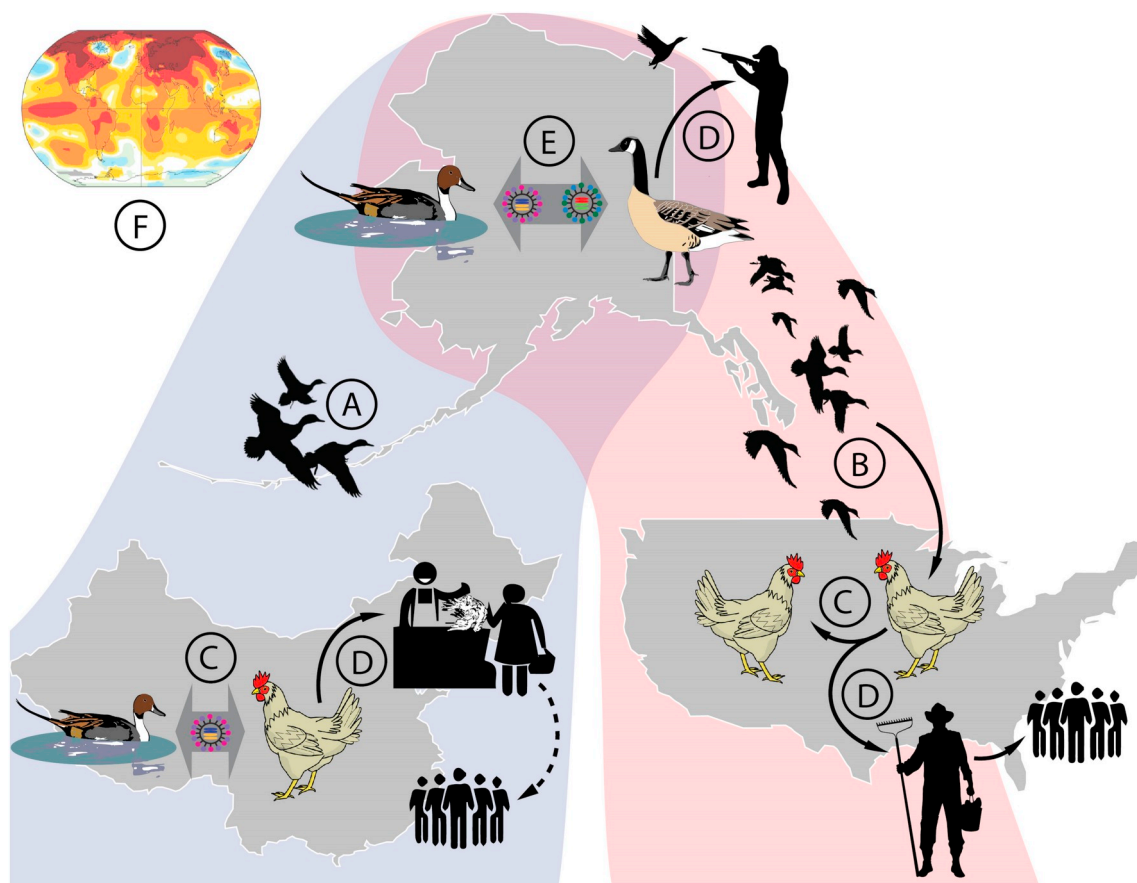


Fig. 1. A. Intercontinental transport and reassortment in which AIV travels via migratory birds from Asia to Beringia via the Australasian and West Pacific migratory flyways (blue).

B. Intra-continental transport and reassortment in which AIV is carried within the North American continent via the Pacific Flyway (red).

C. Local transmission and reassortment in wintering grounds of Asia and the continental United States. In Asia, many domestic poultry farms include natural habitat that is shared with migratory waterfowl, increasing viral sharing between domestic and wild birds. In the United States, there is far less shared habitat between wild and domestic birds, but it is thought that feces dropped by migrating birds may introduce AIV to domestic poultry operations where large, dense avian populations allow rapid viral spread.

D. Potential points of entry into human populations. In China, human outbreaks have been linked to poultry exposure in live animal markets with inconclusive evidence of human-human transmission thus far (dashed arrow). In places where live animal markets are scarcer, poultry farm workers are susceptible to infection, with previous reports of human-to-human transmission (Koopmans et al., 2004). While the potential exists for direct transmission from wildlife to humans via activities such as hunting or wildlife research, this risk is considered to be low. Subsequent transmission of these infections between humans has thus far been very low or nonexistent, causing the greatest direct risk of AIV to humans to be poultry and agriculture.

E. AIV in the environment. Avian influenza virus can persist in water for extended periods of time, increasing the likelihood of viral sharing and reassortment in birds. How this might be affected by climate change is unknown, however.

F. Climate change and Beringia. Warming temperatures cause melting of permafrost, affect water characteristics (availability, temperature, and chemistry), and may alter migratory timing and latitude, changing patterns of avian host overlap and viral sharing. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

affecting agricultural practices in places like China (Gilbert et al., 2017; Yin et al., 2016), driving risk of viral evolution. In this review we identify the avenues through which climate can impact evolution and transmission risk of AIV, and discuss the potential for climate change to alter this risk in the future. We use Fig. 1 to guide this discussion and present data to support our analyses.

As Fig. 1 shows, climate and environmental conditions can impact AIV ecology in several ways, including shifts (spatially and temporally) in wild bird migration routes, alterations in habitats shared between wild and domestic birds (primarily in East Asia), and changes in the ability of the virus to survive in the environment. Our literature review and preliminary analyses support the possibility that warming temperatures in Beringia and East Asia could lead to more frequent introductions of novel strains of avian influenza into North America. Better understanding of the ecological drivers of AIV reassortment and spread can help prepare human populations to reduce exposure risk and thereby help prevent zoonotic transfer of novel flu viruses with

pandemic potential to humans and poultry.

2. Avian influenza ecology

2.1. Intercontinental and intracontinental transport and reassortment (Fig. 1a and b)

Studies have consistently shown the importance of wild migratory birds in dispersal and reassortment of AIV (Saito et al., 2015; Lycett et al., 2016), and the overlap of multiple cross-continental migratory flyways in Beringia makes the region a nexus of viral sharing and transport for Asia and North America (Koehler et al., 2008; Winker and Gibson, 2010). Many phylogenetic studies demonstrate movement and/or remixing of Asian and American strains of AIV through this region. Phylogenetic analysis of the highly pathogenic AIV (HPAIV) H5N8 strain implicated in a 2014 European human outbreak showed likely reassortment and emergence of the virus during summer migration in

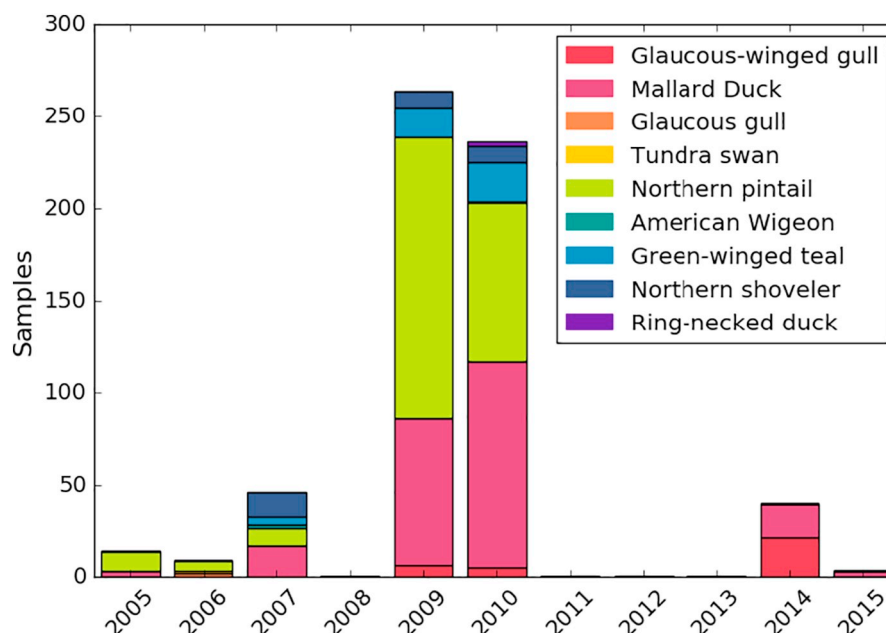


Fig. 2. Positive AIV samples from avian species in Alaska from 2005 to 2015 (data obtained from GISAID).

Beringia (Bouwstra et al., 2015). Another analysis tracked the same strain with origins in China, through Beringia, on to Europe, North America, and East Asia before being discovered in Japan, concluding that dispersal by migrating avifauna was likely (Lee et al., 2015). In a study by Ramey et al. (2015), isolates of AIV from birds in Western Alaska were almost identical to nucleotides of H9N2 virus from China and South Korea, suggesting the virus was introduced to Alaska via migratory birds. Phylogenetic analysis of the H7N9 strain responsible for recent human outbreaks in Southeast Asia shows likely reassortment from Asian flyway migratory birds (which share summer breeding grounds in Beringia), two groups of local chickens, and local ducks (Liu et al., 2013). Phylogeographic analyses of H5N8 HPAIV also suggest transmission from China to the Continental US via wild birds with shared breeding grounds in Beringia (Saito et al., 2015; Lee et al., 2015; Lycett et al., 2016). While one modeling effort described a lower probability of dispersal of an HPAIV strain to North America via migratory birds than by domestic fowl (Kilpatrick et al., 2006), a revision of that model including more accurate wild-bird data contradicts those conclusions (Winker and Gibson, 2010). Recently, HPAIV H5N2 was identified in a mallard (*Anas platyrhynchos*) in Fairbanks, Alaska, providing evidence of maintenance of the virus in North America (Lee et al., 2017). This discovery and recent phylogeographic analyses of HPAIV dispersal have reiterated the importance of migratory birds in the global dynamics of AIV (Lee et al., 2015; Saito et al., 2015; Lycett et al., 2016).

In regard to avian migratory patterns, bandings from separate northern pintail (*Anas acuta*) populations overwintering in Japan and California indicate overlap during the breeding season in Russia, and genetic markers reveal little difference in genetic structure between populations, suggesting they are interbreeding and creating opportunities for pathogen transmission (Flint et al., 2009). More recently, a long-term study showed the importance of both summer and winter breeding grounds of migratory birds in transmission and dispersal of AIV (Samuel et al., 2015).

Although Beringia appears to be a hotspot for AIV transport and mixing (Winker and Gibson, 2010), direct sampling of waterfowl has yielded results that vary by species, timing, and location, both in terms of infection rates and in evidence for viral reassortment. Runstadler et al. (2007) found a 25% positive rate for AIV of mixed antigenic types in ducks sampled in Alaska. A multi-decade study by Krauss et al.

(2004) identified diverse antigenic types within shorebirds and ducks in northern Canada, and highlighted the seasonality of influenza virus in waterfowl. They reported AIV prevalence in ducks of 22.2% during the fall migration and 0.03% on arrival to northern breeding grounds in the spring, contrasting with a 14.2% prevalence in shorebirds upon spring arrival. However, other studies found lower rates of AIV infection. Winker et al. (2007) found only a 0.06% prevalence of mixed antigenic types out of 8254 samples from western Alaska from 1998 to 2004, and Ip et al. (2008) found only 1.7% positive samples from 16,797 samples from 2006 to 2007 with no H5N1 HPAIV strains discovered. In another study by Wahlgren et al. (2008), only 4 of 202 fecal samples (~2%) from wild birds in Alaska were positive for AIV. High rates of seroprevalence, ranging from 30% to > 90% between species, further suggests that indices of low infection rates may be related to the timing of active viral shedding (Wilson et al., 2013). Variation in the temporal-spatial landscape of viral antibody persistence in birds (Samuel et al., 2015; Ip et al., 2008), and differences in species sampling or processing techniques remain significant barriers to meaningful comparison between these sampling efforts (Machalaba et al., 2015).

Notably, many surveillance efforts to date focused on discovery of HPAIV strains with little examination of low-pathogenic AIV (LPAIV) strains. This approach overlooks the important role of LPAIV in global ecology and evolution of AIV. In their sampling of Alaska mallards, Hill et al. (2017) discovered LPAIV that shared ancestry with HPAIV. Pearce et al. (2011) found higher rates of LPAIV in Alaskan trans-hemispheric migrants than in local migrants, and Pearce et al. (2009) found LPAIV with Asian lineages in northern pintails in Alaskan breeding grounds indicating its importance in intercontinental dispersal.

AIV reassortment events are facilitated by the influenza virus' segmented RNA structure, which in conjunction with AIV coinfection rates of 26% of North American wild bird isolates in one study, allows for the constant emergence of new viral subtypes with variable infectivity and pathogenicity (Dugan et al., 2008). Recent identification of “promiscuous” hemagglutinin (HA) clades capable of reassortment with multiple neuraminidase (NA) groups to produce novel HPAIV strains suggests a mechanism for this reassortment (Saito et al., 2015). Additionally, it is notable that the distinction between LPAIV and HPAIV is made based on virulence in domestic poultry (Swayne and Suarez, 2000), which may not be related to the pathogenicity of any given strain of virus in the immunologic landscape of wild avian or human

populations. Furthermore, sampling for avian species that are likely to produce positive samples and for locations that are productive and easier to access may lead to biased findings (Runstadler et al., 2013).

In Fig. 2, we show positive AIV samples from the Global Initiative on Sharing All Influenza Data's (GISAID) EpiFlu database (<http://platform.gisaid.org/epi3/frontend#5eaf93>) for Alaska between 2001 and 2015. Two things are notable from this figure: 1) there is a great amount of variability in the annual number of positive samples in the database, with the vast majority collected during 2009 and 2010; and 2) northern pintails and mallards account for the majority of the positive samples. While these data may indicate higher than normal incidence in 2009 and 2010, they more likely reflect sampling efforts that are uneven in host, time, and geography. This makes it difficult to determine temporal patterns of AIV presence in Beringia. Consequently, identifying relationships between AIV and climate and environmental conditions is also challenging. However, given the findings of increased post-breeding viral prevalence in northern sample sites by Krauss et al. (2004), it follows that warming climate would likely expand the Arctic breeding and post-breeding season for avian migrants. Increased time of individual and population overlap would increase the probability of AIV transmission and reassortment, with the potential for rapid spread in the immunologically naïve juvenile populations (Cappelle et al., 2014; Van Dijk et al., 2014), aiding distribution of novel seasonal strains farther into North America and Asia.

Through transmission and reassortment in Beringia, Asian and novel strains of AIV can be transported by wild birds throughout the Americas, especially along the Pacific Flyway. An analysis of a poultry outbreak in Mexico indicates reassortment from sources in two separate North American flyways (Lu et al., 2014). Scotch et al. (2014) also found evidence of intra-flyway diffusion of AIVs in the southwestern US. When testing AIV infections in waterfowl in Alaska and Central Valley California, Hill et al. (2012) found the diversity of AIV to be higher during winter compared to the breeding season, supporting the hypothesis that migrating birds introduce new viral strains into southern areas, creating more opportunities for reassortment. In a related study of mallards in California, Hill et al. (2012b) found that the migrating birds could introduce AIVs from more northern breeding grounds, although they rarely became widespread. Resident birds, however, maintained continual circulation of a few subtypes. Another analysis of the Pacific Flyway revealed that although the seroprevalence of AIV in wild birds was low, the subtypes were diverse, especially in waterfowl in Central Valley California (Siembieda et al., 2010). In their phylogenetic network analysis of North American AIV sequences, Hill et al. (2016) found evidence that the virus was amplified during summer but that interspecies transmission and reassortment of the virus peaked during winter. They posited that winter migrants introduce the virus to other species during their trips south, where the virus can then be transmitted to other avian networks. In the Netherlands, Van Dijk et al. (2014) observed a similar phenomenon where AIV infection rates in mallards had a small peak in summer due to a large susceptible juvenile population, but the largest peak occurred in autumn with the arrival of migratory birds. In their study of wild birds along the Pacific Flyway, Bevins et al. (2016) detected HPAIV of the H5 clade in 1.3% of birds, mostly waterfowl, and found that most birds were asymptomatic. Asymptomatic carriage enables longer transport distance of the virus because sick birds might be less likely to migrate. While some modeling and phylogeographic analyses found mixed results regarding the spread of HPAIV H5N1 via migratory birds (Kilpatrick et al., 2006), it is clear that the risk of further outbreaks in avian species continues, and shows great potential for breaching geographic boundaries.

2.2. Local transmission and reassortment (Fig. 1c and d)

Land use and local habitats also impact AIV ecology and include dynamics that may be affected by climate change. Past studies demonstrated a correlation between increased urbanization and increased

disease load in avian species (Bradley et al., 2008). Specific to AIV, outbreaks were strongly associated with changes in land use in Southeast Asia. Increasing density of poultry (Chastel, 2004), loss of farmlands and rural areas (Long et al., 2008), changes in land cover with alterations in rice cropping, and free-grazing domestic ducks (Gilbert et al., 2007) were all implicated as mechanistic causes. H5N1 outbreaks in Southeast Asia were associated with lower elevation when controlled for population density and surface-water coverage, likely reflecting warmer temperatures (Martin et al., 2011). Several studies examined ecological factors with land use changes in peri-urban Vietnam and support the interplay of environmental, genetic, ecological, and social factors as the convergence model of emerging infectious disease (Saksena et al., 2015). In support of the interplay of environmental and social drivers of AIV pathogenicity, the recent Chinese H9N2 outbreak is thought to be related to viral changes following antigenic drift in response to the widespread use of influenza vaccinations in poultry farms (Lee et al., 2016; Wei et al., 2016). Belkhiria et al. (2016) used LPAIV surveillance data, wild bird demographics, poultry density, environmental data, and socio-economic data to identify areas of high suitability of LPAIV and used it as a proxy for HPAIV risk in the US. They found that areas in the mid-West and coastal regions were at highest risk, corresponding to 89% of locations affected by the 2014–2015 HPAIV outbreak. An examination of AIV genome sequences by Ren et al. (2016) revealed East and Southeast Asia to be areas of high avian-mammal transmission. Swine and migratory birds were found to be particularly important for spreading the virus through trade and migration routes. However, a study of mallards by Van Dijk et al. (2015) suggested that regional movement of individuals infected with LPAIV was reduced compared to non-infected birds, which may suggest a more limited role in AIV spread.

While migrating wild birds enable long-distance transport of AIV, they can also transmit the virus to domestic poultry (Fig. 1C). Poultry farming operations that are accessible to wild birds increase opportunities for contact between domestic and wild fowl and the possibility of spread to and among human hosts. Although many zoonotic transmissions of AIV from birds to humans have not resulted in subsequent human-human transmission (Wang et al., 2008), at least one avian influenza outbreak produced spread among people after initial transfer from poultry to farm workers (Koopmans et al., 2004). This investigation tested poultry workers, farmers, and family members after an outbreak of H7N7 in poultry farms in the Netherlands revealing transmission to people handling poultry and also evidence of person-to-person transmission. Although the need for further surveillance, education, and preparedness in poultry workers has been documented (Fatiregun and Saani, 2008; Saenz et al., 2006; Flint et al., 2015), interventions have largely been reactive and costly (Arriola et al., 2015). The devastating human outbreaks of AIV in China have been linked to exposure to poultry in live-animal markets (OIE, 2013). In addition to contact with domestic poultry, hunters and wildlife professionals may also have increased exposure to AIV as evidenced by serologic samples that suggest past infection with AIV (Gill et al., 2006). This is of increased concern in Native American and Alaska Natives as well as indigenous Asian populations given the importance of subsistence hunting in some communities, and evidence of increased morbidity and mortality from past influenza pandemics in these populations (Groom et al., 2009; Wenger et al., 2011).

In 2014–2015, the US experienced an outbreak of HPAIV in the West and Midwest that decimated the local poultry industry, resulting in the culling of over 48 million domestic birds and leading to devastating economic losses (Jhung and Nelson, 2015; APHIS, 2014–2015). One model that focused on the wild-domestic avian interface demonstrated the importance of domestic bird culling at the time of outbreak (Pandit et al., 2013). Screening of poultry workers at risk of contact yielded no evidence of human infections, but this surveillance effort required further significant use of resources including use of antiviral prophylaxis (Arriola et al., 2015). While local dispersal is likely

between domestic poultry flocks, local to wild bird transmission can precipitate into large-scale dispersal via migratory birds that can introduce the virus into the domestic poultry population in new regions (Bahl et al., 2016).

2.3. AIV in the environment (Fig. 1e)

Fresh water in temperate and Arctic areas may play important roles in viral spread, and warming of arctic and subarctic regions may increase or decrease habitat suitability for AIV persistence outside of hosts. Numerous studies support the likely persistence of AIV in Arctic freshwater environments. Ramey et al. (2010) posited that foreign AIV gene segments are partially maintained in Alaska in the environment. Using an epidemiological SIRS (susceptible, infected, recovered, susceptible) model parameterized using bird counts and AIV prevalence data, Roche et al. (2009) found transmission patterns were dominated by water-borne processes. However, the length of the virus' viability in water depended on a number of factors. Control studies found that ambient aquatic viral persistence is strongly influenced by temperature, with higher persistence at lower temperatures and with higher persistence in freshwater than saltwater (Stallknecht et al., 1990; Stallknecht et al., 1990b). Other studies found similar results but identified the potential importance of biological material in the water (Domanska-Blicharz et al., 2010). Davidson et al. (2010) found that lower water temperatures ($\sim 4^{\circ}\text{C}$) favored survival over intermediate and high temperatures (20°C and 37°C respectively), but they also found acidic water (pH 5) to be especially detrimental to virus survival compared to more basic water (pH 7) at the same temperature. Additionally, Keeler et al. (2014) found water that was more neutral/basic ($> 7 \text{ pH} < 8.5$) vs acidic/basic ($\text{pH} < 7$ and $\text{pH} > 8.5$), with a low ammonia concentration, to be more favorable for the persistence of AIV in surface water samples. The favorable combination of low water temperatures ($< 17^{\circ}\text{C}$), neutral-basic pH (7.4–8.2), and low salinity (0–200,000 ppm) for viral persistence was also observed by Brown et al. (2009). The complex interplay of aquatic temperature, acidic-basic chemistry, and co-existing biota and salinity in natural systems precludes predictions regarding the effects of climate on AIV environmental persistence given current knowledge. And while Arctic ocean temperatures have and are likely to continue to rise (Carmack and McLaughlin, 2011) and pH has decreased and will likely continue to decrease (Steinacher et al., 2009) the changes are unlikely to be sufficiently large to impact AIV survival.

3. Climate change and AIV (Fig. 1f)

3.1. Climate change impacts on AIV ecology in Asia

Agricultural systems are susceptible to alteration with climate change, and as we discussed in Section 2.1, are an integral component of AIV ecology because they facilitate interactions between domestic and wild birds and enable the spread of the virus through poultry trade (Muzaffar et al., 2010; Gilbert et al., 2017). These systems are changing, especially in East Asia, with consequential impacts on disease risk from climate and social drivers such as increasing population density, migration to urban centers, alterations in diet, changes in land use and agricultural practices, warming temperatures, and shifting precipitation patterns (Liu et al., 2014; Gilbert et al., 2017). China is especially important in AIV ecology and evolution because it has the world's largest populations of chickens and ducks (Artois et al., 2017). Murdiyarso (2000) reviewed many of the climate-change driven agricultural alterations and adaptations in Asia, including change in rice yields due to rising temperature, transformed agricultural land patterns due to altered precipitation, and shifts in agricultural land to more marginalized areas due to conflicts between new areas of agricultural suitability and existing land use. Satellite imagery has revealed an increase in paddy rice in northeastern China, likely due to population expansion

but also warming temperatures expanding the growing season (Dong et al., 2015; Yin et al., 2016; Zhang et al., 2017). Expansion further northward in farmland suitability for paddy rice could continue under projected warming scenarios (Zhang et al., 2017b). Zhang et al. (2014) presented evidence for earlier H5N1 outbreaks in domestic poultry with higher temperatures over the course of 6 years. These changes all have implications for AIV ecology. The strong association between free-ranging ducks and rice-crop intensity (Gilbert et al., 2017), the connection between migrating ducks and AIV circulation and outbreaks (Cappelle et al., 2014), and the association between HPAIV outbreaks and live-poultry markets (Artois et al., 2017) reveal avenues for changes in AIV risk in the face of agricultural and social changes in Southeast Asia. Variables such as climate, land cover, human population, agriculture, and poultry production are already being combined with surveillance data to identify potential hotspots for emerging AIV risk that include northern India, central and coastal China, the western Korea Peninsula, southwestern Japan, and the Nile Delta. Emergence of AIV outbreaks in this heavily populated region could increase the potential for viral reassortment between avian and human virus strains, a source of pandemic risk (Fuller et al., 2013).

3.2. Climate change impacts on AIV ecology in Beringia

Beringia is critical to the global disease ecology of AIV, and the Arctic ecosystem is susceptible to impacts from changing climate. Specific evidence of melting of permafrost over 100 years, and increasing groundwater and lake temperatures over the past 40 years (Hinzman et al., 2005), with changes leading to water temperature variation of up to 3°C , are considered significant for wildlife disease dynamics (Kyle and Brabets, 2001). There is also specific evidence that warming temperatures may lead to increased AIV pathogenicity or transmissibility. Tian et al. (2015) calculated risk of H5N1 outbreaks (2005–2009) using climate and migratory bird data and found that 1) minimum daily winter temperature and maximum daily summer temperature influenced bird migration patterns; 2) high mean air pressure and low mean specific humidity indicated higher risk for H5N1 outbreaks in migratory birds; and 3) projected changes in climate could increase risk of H5N1 in Western countries. Using environmental variables and surveillance data on wild bird infections, Herrick et al. (2013) created a global model of AIV risk by identifying the niche where outbreaks were most likely to occur. Northern climates, especially those with low rainfall and low temperatures, held the highest probability of an outbreak in wild birds, further supporting the potential importance of Beringia in spreading and reassortment of AIV (Herrick et al., 2013). In Fig. 3, we show our analysis of projected changes in temperature in Beringia and related regions between the time periods 1986–2005 and 2021–2040. This analysis illustrates that higher latitudes are warming faster than the rest of the planet. This would be expected to have implications for wildlife ecology (described below) and possibly viral persistence in the environment.

3.3. Climate change impacts on bird migration

Climate variability has been shown to change the distribution, composition, and migration patterns of wild birds important for the mixing of AIV (Gilbert et al., 2008). A long-term study found earlier seasonal avian migrant arrival associated with warming temperatures over the past 50 years (Ward et al., 2016), and modeling studies projected loss of shorebird breeding habitat leading to compositional changes in flyway and breeding ground overlaps (Wauchope et al., 2016). Van Hemert et al. (2014) suggest that the accelerated warming of the Arctic could result in novel species assemblages and promote increased pathogen transmission, but noted that much more research in this area is warranted. Winker and Gibson (2018) provided an initial species-level analysis for Beringia. In their review of climate change effects on avian migratory patterns, Patterson and Guérin (2013) noted

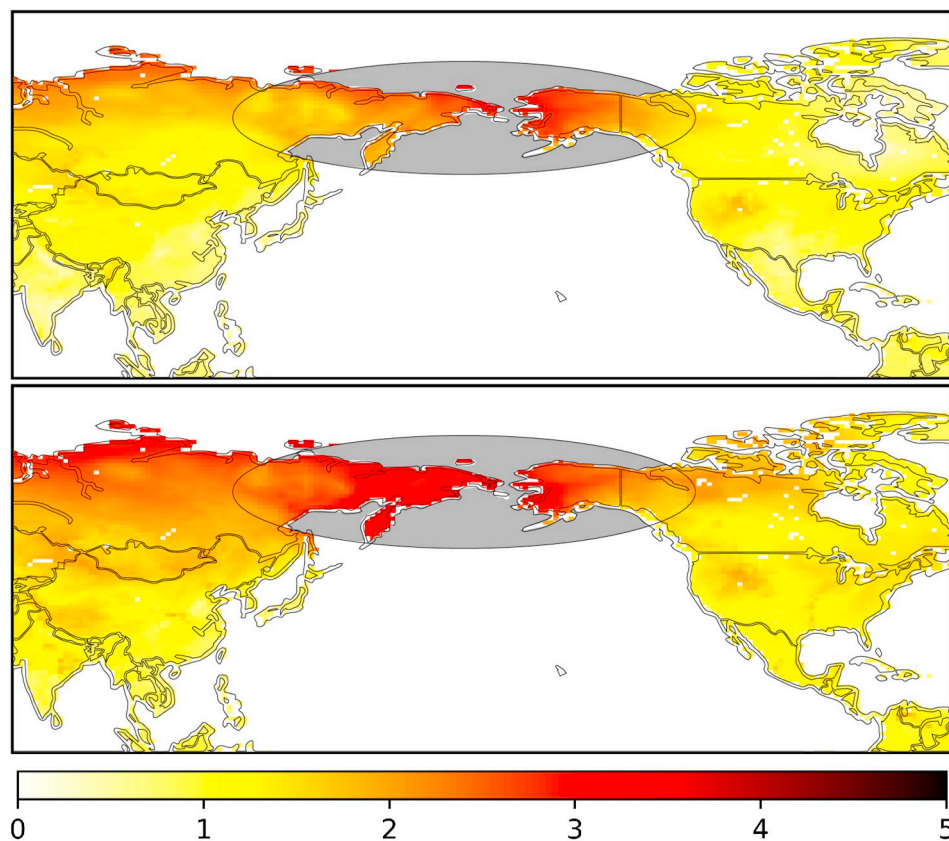


Fig. 3. Change between historic (1986–2005) and projection of future (2021–2040) temperature (°C) from the Coupled Model Intercomparison Project 5 (CMIP5) using RCP4.5 (top) and RCP8.5 (bottom) and the Community Climate System Model 4.0 (CCSM4) with the approximate area of Beringia highlighted in grey.

a change in avian phenology (timing of biological events), a poleward shift in avian distributions, and changes in the patterns of avian movement. In an attempt to develop a population model for avian migrant species, James and Abbott (2014) discovered that climate change can potentially alter migratory species populations, but that the interactions between phenological changes and migration distance determined the overall impact. Photoperiod, temperature, food availability, and nesting sites all influence avian migration and reproduction; however, photoperiod is not regulated by climate and the timing of the other factors may not change synchronously (Carey, 2009). Miller-Rushing et al. (2008) noted that short-distant migrants responded to temperature, while long long-distant migrants exhibited more stable migration timing. Mayor et al. (2017) found that in the US, shifts in migration vary regionally and that the timing did not always synch with other phenological changes. For example, Lameris et al. (2017) suggested that warming Arctic temperatures could reduce nitrogen-rich forage for migrating birds and both advance and reduce the peak in food availability, which could reduce reproductive fitness. Furthermore, some species and populations are non-migratory and therefore their responses to climate change will be different (Carey, 2009). Charmantier and Gienapp (2013) found little evidence that climate change is advancing avian phenology through evolutionary means, although this does not preclude intra-generational behavioral changes that could be strongly affected by climate. First-arrival dates are often used to determine changes in avian migration patterns; however, Goodenough et al. (2015) found a relatively weak although significant correlation between first arrival dates and mean arrival dates for long-distance migrants. Miller-Rushing et al. (2008) also noted that climate-driven changes in migrant population sizes may cause inaccuracies in calculations of arrival dates.

The variability in responses to climate change among species and regions is likely to alter the makeup of avian communities. The ultimate

impact that climate change will have on avian migration, and consequently AIV ecology, is difficult to determine due to many factors influencing migration and the independent responses of species and populations to climate. Still, the timing of these events can be important for AIV transmission. Model results demonstrated that for a particular habitat, the avian species both likely to introduce, and be most susceptible to AIV could change seasonally (Alba et al., 2012). Cappelle et al. (2014) noted that in China free-ranging domestic duck farming often produce juveniles, who are often naïve to and susceptible to AIV, during wild-duck migration and therefore can act to amplify the virus and facilitate transmission between domestic and wild populations. Although future shifts in migration timing may alter this phenomenon, the already expanding growing season and changes in cultivation timing and irrigation (Yin et al., 2016) may broaden the window during which these overlaps occur, increasing AIV transmission. Changes in agricultural patterns can increase contact between domestic and wild migratory ducks as the latter are forced into these areas during their migration stopovers due to human encroachment into natural wetlands and forests (Klaassen et al., 2012).

In Fig. 4, we show our analysis of northern pintail observations (based on data from eBird.org, 2001–2015) in Alaska regions alongside winter/spring temperatures (Global Land Data Assimilation Systems, 2001–2015). The observations exhibit seasonal and geographic trends that are largely consistent with temperature patterns. Colder regions, like North Slope and Nome, demonstrate waterfowl observations over a more limited time period, with the earliest observations recorded in May and the latest in September. In warmer locations, observations are more dispersed throughout the year, especially in Juneau where observations were made during every month of the year. These observations indicate a strong relationship between temperature and the presence and migration of northern pintails. The association between longer periods of observations and warmer temperatures suggests that

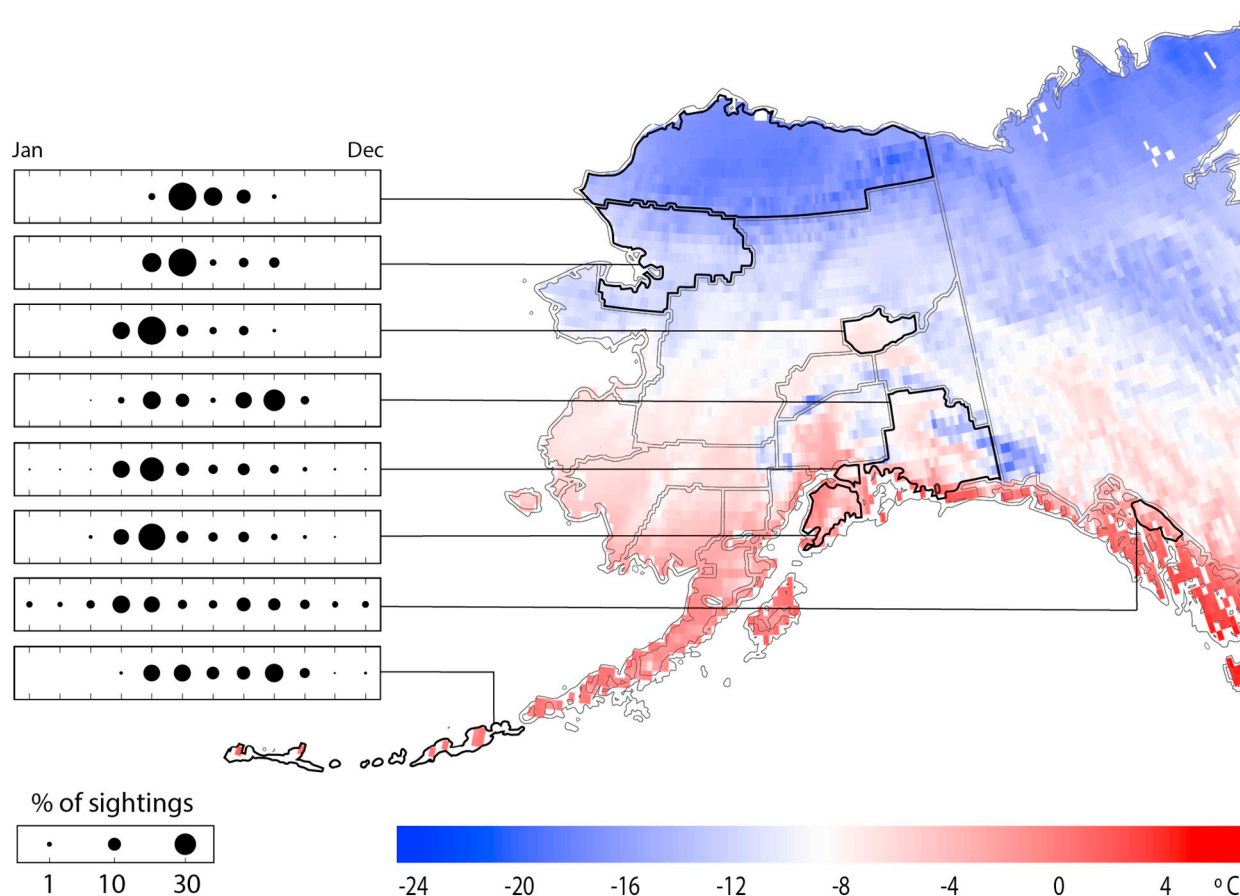


Fig. 4. Monthly sightings of northern pintails (*Anas acuta*) in relation to location and average temperature in Alaska. Color mapping represents a 15-year average surface temperature for the months of January to May (when the birds generally arrive) from 2001 to 2015. Monthly bird sightings by region are averaged over the same time period. Notably, sightings at more northern, colder locales appear in a much more restricted time band than do sightings at more temperate latitudes. Regions (some of which are boroughs) from top to bottom are: North Slope, Nome, Fairbanks North Star, Valdez-Cordova, Kenai Peninsula, Juneau, and Aleutians West.

as temperatures warm in Beringia, there will be more opportunity for viral mixing in seasonal populations of waterfowl from Asia and North America that spend greater time in contact.

Although there is potential for a warming climate to change patterns of avian migration and ambient conditions in which viruses persist, there is a lack of understanding about how these factors affect the dispersal and mixing of AIV strains (Gilbert et al., 2008). The effects of climate change on avian migration and avian influenza epidemiology are difficult to study and have thus far been overshadowed by investigation into more tangible factors affecting viral hotbeds in East Asia. However, all the factors considered here are likely to change the dynamics of migratory bird interactions, further altering viral transportation, transmission, and intermixing. Still, some lessons can be teased out from recent research. Ramey et al. (2018) reviewed five lessons learned from HPAIV in North America, including 1) wild birds may disperse AIV between North American and adjacent regions, 2) HPAIV can be introduced into wild birds in North America, 3) HPAIV may be transmitted from wild birds to domestic birds, 4) HPAIV can be extremely difficult to detect in wild birds, and 5) wild-bird population immunity might be an important driver of HPAIV outbreaks in North America. Effective surveillance requires a large amount of sampling for HPAIV in a diverse range of species and in important regions such as northern Europe, Russia, and northern China (Verhagen et al., 2015). The importance of Beringia and East Asia as a viral mixing zone affecting disease evolution and spread, and as a portal for disease transfer between East Asia and the Americas, cannot be overstated, especially in the context of a changing climate.

4. Conclusions

While AIV has been studied extensively, there is still uncertainty as to how climate change will impact the ecology of the virus and alter disease risk to human and animal populations. Major surveillance efforts have been sporadic and/or focused on a recent outbreak strain rather than on a broader view of the phylogenetic landscape of HPAIV and LPAIV from which new pathogenic strains continually emerge (Machalaba et al., 2015). Additionally, a lack of knowledge regarding indirect contact-exposure variables for zoonotic transmission of AIV to humans (Rabinowitz et al., 2010) requires further research into the effects of changing climate, land use, and ecological/evolutionary drivers of avian influenza transmission on human pandemic risk (Vandegrift et al., 2010). The importance of a “One Health” approach to avian influenza that considers the interactions of human, animal, and environmental factors has been highlighted (Okello et al., 2014), and our analyses presented in this paper support the need for such an integrated approach. While devastating outbreaks of AIV have occurred in birds recently, the mechanisms and drivers of AIV introduction and evolution in the New World remain obscured at least in part by reactive and intermittent past surveillance efforts.

Many questions therefore remain regarding key aspects of avian influenza ecology and evolution, including the interactions between variables such as changing land use and demographics in Southeast Asia, warming in the Arctic, flyway location and interspecies mixing, interactions between wild birds and farmed poultry, and the role of preventive measures on poultry farms. Exploring these knowledge gaps

will be critical to efforts to improve preparedness and prevention for pandemic influenza.

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Competing interests

The authors declare that they have no competing interests.

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